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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,706	01/28/2005	Verena Stangl	2958-128	7467

6449 7590 08/21/2007

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
08/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,706	STANGL ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

1. Claims 1-12 and 27-29 are pending. Claims 13-26 were cancelled in the amendment filed 7/6/2007. Claims 10-12 are withdrawn for pertaining to a non-elected invention. The elected species MG132 (see the reply filed on 10/10/2006) reads on claims 1-6, 8, 9, and 27-29. Because a prior art rejection is made on this species, the search was not extended to other compounds in the genus of proteosome inhibitors.

Specification

2. The specification is objected to because the heading "Brief Description of the Drawings" is required above the description of Figure 1 on page 11.

Claim Rejections - 35 USC § 101/112

3. The rejection of claims 1-9 under 35 U.S.C. 101 and 112, second paragraph, is withdrawn in light of the amendment filed 7/6/2007.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diseases associated with endothelial dysfunction, does not reasonably provide enablement for a method of preventing diseases associated with endothelial dysfunction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims. The claims are drawn to a method of preventing diseases associated with endothelial dysfunction by administering a proteosome inhibitor. The full scope of the claimed methods includes the complete elimination of all occurrences of a disease in all patients for the entire course of their lives. The prior art does not recognize a single therapy that can completely prevent diseases such as atherosclerosis, heart failure, myocardial infarction, leg ischemia and ischemic diseases of organs such as kidney, spleen, brain and lung. The specification provides no guidance or working examples illustrating that the claimed method is capable of producing this outcome. Thus, there would be undue burden on the skilled artisan to practice the full scope of the claimed methods.

6. Claims 1-9 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

7. Claims 1-9 and 27-29 are drawn to proteosome inhibitors. The specification discloses the complete structure of MG132, MG115, LLnL, PS1, carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon, NLVS, pyrazyl-CONH(CHPhe)CONH(Chisobutyl)$B(OH)_2$,

benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester, PS-314, PS-519, aclacinomycin A, lactacystin, clastolactacystein, PS-273, PS-293, PS-296, PS-303, PS-321, PS-334, PS-352, PS-383, PS-341, PS-1, PS-2, PS-519, epoxomicin, eponenycin, catchin-3-gallate, DFLB, MG273, SEQ ID NOs: 2-5, dihydroeponemycin, omuralid, ALLN, DCI, pefaclock SC, TMC-95-A, gliotoxin, EGCG, ritonavir, lovastatin, aclarubicin, and cyclosporin as examples of proteosome inhibitors. The claims are also drawn to the following partially-defined structures: peptide aldehydes, peptide boronates, peptide vinylsulfones, peptide epoxyketones, peptide α-ketonaldehyde, indanonpeptides, peptide derivatives with C-terminal expoxy keton structures, and modified peptide aldehydes. The minimal structural requirements for these classes of compounds are that they include a peptide sequence and an aldehyde, boronate, vinyl sulfone , epoxyketone, ketoaldehyde, or C-terminal epoxy ketone. An infinite number of peptide compounds could satisfy these minimal requirements. The specification fails to provide additional information about the physical/chemical properties and structure/function relationship for peptide sequences that fall within the genus of proteosome inhibitors. Likewise, the minimal structural requirements for α-ketonamides, polyalkylenaldehydes, polyphenols, β-lacton-derivatives, glyoxal residues and boric acid residues, to which the claims are also drawn, are that the compounds include these chemical moieties plus any additional structure. The specification fails to provide additional information about the physical/chemical properties and structure/function relationship for α-ketonamides, polyalkylenaldehydes, polyphenols, β-lacton-derivatives, glyoxal residues and boric acid residues that fall within the genus of proteosome inhibitors. Accordingly, in the absence of sufficient recitation of distinguishing identifying

characteristics, the specification does not provide adequate written description of the claimed genus.

8. With the exception of MG132, MG115, LLnL, PS1, carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon, NLVS, pyrazyl-CONH(CHPhe)CONH(Chisobutyl)$B(OH)_2$, benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester, PS-314, PS-519, aclacinomycin A, lactacystin, clastolactacystein, PS-273, PS-293, PS-296, PS-303, PS-321, PS-334, PS-352, PS-383, PS-341, PS-1, PS-2, PS-519, epoxomicin, eponenycin, catchin-3-gallate, DFLB, MG273, SEQ ID NOs: 2-5, dihydroeponemycin, omuralid, ALLN, DCI, pefaclock SC, TMC-95-A, gliotoxin, EGCG, ritonavir, lovastatin, aclarubicin, and cyclosporine, the skilled artisan cannot envision the detailed chemical structure of the proteosome inhibitor. Although the minimal structural requirements of the broad genus are defined, there are too many undefined structural features for the skilled artisan to know specifically which compounds possess the claimed functional characteristics. Therefore, these specifically recited compounds, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 5 and 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Regarding claim 5, the term "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

12. Regarding claim 6, the phrase "such as" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

13. The rejection of claims 1-6, 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Sherman *et al.* (U.S. Patent No. 6,096,711) is withdrawn in light of the amendment to the claims filed 7/6/007. Sherman *et al.* do not teach the administration of a proteosome inhibitor in the nanomolar range.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-6, 8, 9 and 27-29 are rejected under 35 U.S.C. 102(b) as being unpatentable over Sherman *et al.* (U.S. Patent No. 6,096,711). The rejection of claims 13-19 and 21-23 is

moot because the claims are cancelled. Sherman *et al.* teach a method for treating pathologies such as ischemic cerebral infarction, ischemic acute renal failure, intestinal ischemia, and ischemic heart disease comprising administering a proteasome inhibitor to the patient (claims 8 and 12-15). The proteasome inhibitor taught by Sherman *et al.* for use in the method is the elected species MG132. In addition, Sherman *et al.* teach that the administration of a proteasome inhibitor during atherosclerotic disease of epicardial coronary arteries or myocardial infarction can minimize damage and provide a therapeutic window for surgical intervention (column 6, lines 1-12). Sherman *et al.* do not teach the use of nanomolar concentrations of MG132. Because the concentration of a drug is a result-effective variable, it would have been obvious to the skilled artisan to optimize the concentration through routine experimentation. See MPEP 2144.05. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

17. In the response filed 7/6/2007, Applicant traverses the rejection on the grounds that Sherman *et al.* does not disclose or suggest the use of the proteosome inhibitot to enhance the expression of eNos. Sherman *et al.* does not explicitly disclose this effect. However, because the active steps of the method taught by Sherman *et al.*, the administration of MG132 to patients suffering from pathologies such as ischemic cerebral infarction, ischemic acute renal failure, intestinal ischemia, and ischemic heart disease, and the chemical structure of the administered compound MG132, are identical to the claimed invention, there is a reasonable expectation that the method taught by Sherman *et al.* would meet this functional limitation. The discovery and characterization of properties of a known material do not make it novel (see MPEP § 2112). Furthermore, there is no requirement that a person of ordinary skill in the art would have

recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP § 2112). If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01. Examiner cannot however determine whether or not the method taught by Sherman *et al.* inherently possesses properties which anticipate or render obvious the claimed invention but has basis for shifting the burden of proof to applicant as in *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). See MPEP § 2112.

18. In the response filed 7/6/2007, Applicant also traverses the rejection on the grounds that there is no suggestion or teaching in Sherman *et al.* that the drug should be administered for the disclosed purposes in the nanomolar range. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1396 (2007) forecloses the argument that a specific teaching suggestion or motivation in the prior art is required to support a finding of obviousness. Sherman *et al.* establishes dose of the drug MG132 as a result-effective variable. Therefore, it would be obvious to the skilled artisan to optimize the dose used in the method.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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